INDIA NON JUDICIAL

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Certificate of Stamp Duty

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Description of Document	:	Article 5(h) Agreement (not otherwise provided for)
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Second Party	:	PIA AND PIAR PARUL UNIVERSITY
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Date : 7/9/21

A.C.C. R.U. PARMAR • VAGHODIA •

NOTARY
Name
RAVJIBHAI PARMAR
Area Ta. Vaghodia,
Dist. Vadodara.
Reg. No. 953 / 2009
GOVT. OF GUJARAT (INDIA)

NOTARIAL

KC 0007254641

Statutory Alert:
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per ANNEXURE I (IA, IB, IC & ID)

Memorandum of Understanding

This Memorandum of Understanding (MOU) is made and executed at Mumbai on this 27th day of August 2021, between Solumiks Herbaceuticals Limited, a Company incorporated under the Companies Act, 1956, having its registered office at 135, Nanubhai Desai Road, Khetwadi, Mumbai – 400004, hereinafter referred to and called as "SPONSOR",

And

And

1. Parul Institute of Ayurved, Faculty of Ayurved, Parul University, At & Po - Limda, Taluka- Waghodia, District - Vadodara, Gujarat, Pin code – 391760,

2. Parul Institute of Ayurved and Research, Faculty of Ayurved, Parul University, At & Po - Ishwarpura, Taluka- Waghodia, District - Vadodara, Gujarat, Pin code – 391760,

Hereinafter referred to and called as "INSTITUTE" and has fully established good research facilities and hospital facility for the clinical studies in the field of Ayurved and Ayurvedic Drugs.

WHEREAS, the SPONSOR is an Ayurved company involved in research, development, manufacture and sale of medicines for use in humans.

WHEREAS, the SPONSOR contacted the INSTITUTE to provide formulation development & pharmacological study support.

WHEREAS, the SPONSOR and INSTITUTE are concerned with the diagnosis, treatment and prevention of disease and/or clinical research for the improvement of healthcare;

The Parties represent and warrant that they each have the authority to enter into this MOU. In consideration of the undertakings and commitments set forth herein, the Parties agree to enter into this Collaborative Research Project MOU.

PROTOCOLS

The scope and nature of the Projects to be performed will be in accordance with the protocol agreed between the SPONSOR and INSTITUTE. "Protocol" means the document signed by the Authorised Representative of the INSTITUTE, detailing all aspects of the collaborative research project. This protocol fully details the study activities and responsibilities to be undertaken.

OBLIGATIONS

INSTITUTE and the SPONSOR agree to provide the aforestated Protocols as per **ANNEXURE I (IA, IB, IC & ID)** accompanied by services referred above at the onset for the following research projects of the SPONSOR:

IA. An Open Labelled phase 4 Single Group Proof-of-concept study to evaluate the Efficacy & Safety of Arshkeyt, a 7 day kit in patients suffering from Anal fissures.

IB. A prospective, randomized, comparative, parallel, 2- arm study to evaluate the efficacy and safety of a Myostaal liniment application as add on therapy for the reduction of spasticity in patients suffering from Hemiplegia.

IC. A prospective, randomized, comparative, parallel, 2-arm study to evaluate the efficacy and safety of a Myostaal liniment application as addon therapy for muscle strengthening in patients suffering from osteoarthritis of knee.

ID. Clinical study to evaluate effect of Menocramp Tablets in the management of Primary Dysmenorrhoea.

INSTITUTE shall prepare final report in writing and publication of the manuscript based on the data generated.

The SPONSOR shall be responsible for providing the funds required for the Projects as per **ANNEXURE II (IIA, IIB, IIC, & IID)** as mutually agreed between the parties.

PAYMENT

Total cost of the Projects would be as agreed upon by both the parties. Payment shall be made by the SPONSOR to the INSTITUTE in the favour of: 1. Parul University (IEC Fee - Parul Institute of Ayurved), 2. Parul Institute of Ayurved Research (IEC Fee - Parul Institute of Ayurved and Research) & 3. R and D Centre Unit of Parul University by cheque or DD or NEFT payable at Mumbai, against the invoice raised by the INSTITUTE.

CONFIDENTIAL INFORMATION

In consideration of the mutual promises and MOU contained herein, the sufficiency of which are hereby acknowledged by both parties, it is hereby agreed as follows:

a. The Parties agree to adhere to the principles of confidentiality during the term of this MOU as well after the conclusion of the same.

b. The INSTITUTE further undertakes to treat as strictly confidential and not to disclose to any third party any Confidential Information of the SPONSOR.

c. The INSTITUTE undertakes not to make use of any Confidential Information of the SPONSOR, other than in accordance with this MOU, without the prior written consent of the SPONSOR.

d. In consideration of this potential access to confidential materials, INSTITUTE agrees that INSTITUTE including its employees, students and associates shall hold and keep secret all such information about the SPONSOR or the SPONSOR's Client List.

PUBLICATIONS & PRESENTATIONS

It is the intent of the parties that no publication shall contain any of confidential information disclosed by SPONSOR without SPONSOR's prior written permission.

No data shall be published in any scientific or non-scientific journal, newspaper or any other mass-media source in or out of India without prior written consent from SPONSOR.

ASSIGNMENT TO OTHER PARTIES

The parties hereto shall not transfer or assign any of their rights and obligations under this MOU to any other party without obtaining prior consent in writing from the SPONSOR.

TERM / DURATION OF MOU

This MOU shall be initially valid for a period of one year from the date of signing of this MOU and the confidentiality clause agreed to between the parties shall survive after the cessation of duration or termination of MOU. The Parties may extend the term of this MOU for additional periods as desired under mutually agreeable terms and conditions which shall be reduced to writing and signed by the Parties.

INTELLECTUAL PROPERTY AND COMMERCIAL RIGHTS

Intellectual property rights for the Project such as title to all inventions, discovery, development or other intellectual property, including not limited to copyrights, patents, shall reside with the SPONSOR. The INSTITUTE shall not hold any intellectual, commercial, or marketing rights of the Projects. These shall lie solely with the SPONSOR alone.

OBLIGATIONS OF THE INSTITUTE

i. The INSTITUTE accepts and signs the terms and conditions for the study provided by the SPONSOR.

ii. The INSTITUTE shall be responsible for all commitments from the INSTITUTE, communicated to the SPONSOR, in writing.

iii. The documentation and interpretation shall be in tune with the requirements of the project.

iv. The project coordinator/s and the Principal Investigator are responsible for secrecy and confidentiality of the process and materials used in the project. This MOU also acts as Non-Disclosure" arrangement of the project details for perpetual period.

TERMINATION

This MOU commences on the Effective Date and shall continue in force for one year but may be terminated:

i) If the INSTITUTE defaults on any material term of this MOU,

ii) Adherence to the protocol is poor or data recording is chronically inaccurate or incomplete.

However, The SPONSOR shall be at liberty to terminate the MOU by giving one month advanced written notice to the INSTITUTE, without assigning any reason.

The INSTITUTE may terminate this MOU prior to completion of the Project by written notification upon SPONSOR's material default of its/their obligations hereunder; provided that the INSTITUTE shall allow the SPONSOR thirty (30) days from the date of notification to cure such default.

In event of termination of this MOU at the instance of the INSTITUTE or due to INSTITUTE's defaulting of any material term of this MOU or non-adherence of the protocol, the SPONSOR shall not liable to pay any compensation or damage to the INSTITUTE. However, if the SPONSOR on its own accord terminates the MOU for other reasons not attributable to the performance of the INSTITUTE, the SPONSOR agrees to compensate the INSTITUTE on proportionate basis after evaluating the projects.

At close-out of the project/s following termination or expiration of this MOU the Parties shall upon request immediately deliver to the other Party all Confidential Information, except for copies to be retained in order to comply with Institution's archiving obligations or for evidential purposes. Termination of this MOU will be without prejudice to the accrued rights and liabilities of the Parties under this MOU.

MISCELLANEOUS

This MOU shall be binding upon the parties, their legal representatives, successors and assignees; may not be amended except by written instrument signed by the parties. Nothing shall be construed as creating a joint venture, partnership or contract of employment between the Parties.

ARBITRATION, APPLICABLE LAW AND JURISDICTION

i) Any disputes between the parties shall be resolved by mutual discussions. Unresolved disputes, if any, shall be subjected to Arbitration under the Arbitration and Conciliation Act, 1996 wherein each Party can appoint one Arbitrator and the two Arbitrators will thereupon decide Presiding Arbitrator. The venue of arbitration shall be Mumbai. The decision of the arbitrator shall be binding on both parties.

ii) This MOU shall be governed by the Laws of India and subject to the jurisdiction of Courts in Mumbai.

iii) This MOU supersedes all other representations, understandings or communication whether written or verbal, with respect to the subject matter hereof.

In witness whereof, the parties hereto have executed this MOU by their duly authorized representatives.

Read and Understood:

SPONSOR

Ranjit Puranik
Managing Director
Shree Dhootapapeshwar Limited
135 Nanubhai Desai Road. Khetwadi
Mumbai – 400004.

INSTITUTE

Dr. Hemant Toshikhane
Dean & Principal, Parul Institute of Ayurved
Faculty of Ayurved,Parul University,
At & Po - Limda,
Taluka- Waghodia, District - Vadodara,
Gujarat, Pincode – 391760

Dr. Bhagawan G Kulkarni
Principal, Parul Institute of Ayurved and Research,
Parul University, AP Iswarpura, Tal – Waghodia,
Vadodara, Gujarat 391760

Witnesses:

1. Dr Mukesh B Chawda
   Senior Manager - Medical Services
   Solumiks Herbaceuticals Limited
   135 Nanubhai Desai Road
   Khetwadi, Mumbai - 400 004.

2. Mr Vijay Zagde
   Manager - Accounts
   Solumiks Herbaceuticals Limited
   135 Nanubhai Desai Road
   Khetwadi, Mumbai - 400 004.

3. Dr. Shailesh Vinayak Deshpande
   Professor, Department of Kayachikitsa,
   Parul Institute of Ayurved, Parul University,
   AP Limda, Tal – Waghodia,
   Vadodara, Gujarat 391760

4. Dr. Akshar Ashok Kulkarni,
   Associate Professor, Department of Kriya Sharir,
   Parul Institute of Ayurved and Research,
   AP Ishwarpura, Tal – Waghodia, Vadodara
   Gujarat 391760

NOTARY
Name : RAVJIBHAI U. PARMAR
Area : Ta. Waghodia, Dist. Vadodara.
Reg. No. 953 / 2009
GOVT. OF GUJARAT (INDIA)

ATTESTED
RAVJIBHAI U. PARMAR
NOTARY (Govt. of Gujarat)

My Commission Expires on
Dt. 26-02-2024
RAVJIBHAI U. PARMAR
NOTARY (Govt. of Gujarat) INDIA

Annexure IA

Study Protocol

Protocol title: An Open Labelled Single Group Proof-of-concept study to evaluate the Efficacy & Safety of Arshkeyt, a 7 day kit in patients suffering from Anal fissures.

Name and address of the sponsor: Solumiks Herbaceuticals Ltd
135 Nanubhai Desai Road, Khetwadi,
Mumbai - 400 004

Principal investigator

1) Dr Vivekanand Kullolli
Professor, Department of Shalya Tantra, Parul Intitute of Ayurved, Parul University

Co-investigator

1) Dr. Khemchandra Mahajan
Professor, Department of Shalya Tantra, Parul Intitute of Ayurved & Research, Parul University
2) Dr. Shailesh Jaiswal
Associate Professor, Department of Shalya Tantra, Parul Intitute of Ayurved, Parul University
3) Dr. Tejas Patel, Consultant Surgeon, Parul Sevasharam Hospital, Parul University

Trial site(s):

Site 1: Parul Institute of Ayurved, Parul University, AP Limda, Tal Waghodia, Vadodara, Gujarat 390019

Site 2: Parul Institute of Ayurved and Research, Parul University, AP Ishwarpura, Tal Waghodia, Vadodara, Gujarat 390019

Clinical laboratory

Site 1: Central Laboratory, Parul Ayurved Hospital, Parul University, AP Limda, Tal Waghodia, Vadodara, Gujarat 390019

Site 2: Central Laboratory, Parul Institute of Ayurved and Research, Parul University, AP Ishwarpura, Tal Waghodia, Vadodara, Gujarat 390019

Study objectives

Primary Objective:

Number of patients of anal fissure showing a 90% or more reduction in the composite score at the end of week 6.

Secondary Objective:

1. **To compare the pre and post composite scores at the end of week 6.**
2. **To compare the patient's global impression score at 6 weeks.**
3. **To compare the Physician's global impression score at 6 weeks.**
4. **To compare the efficacy in reducing the pain on defecation (based on a 10-point VAS) from baseline to 6 weeks.**
5. **To compare the efficacy in decreasing the severity of bleeding from baseline to 6 weeks.**
6. **To compare the efficacy in healing anal fissure wounds from baseline to 6 weeks.**
7. **To assess the adverse event profile (local and systemic).**

Study Design

A single centre, open labeled, single group, proof-of-concept study in patients of anal fissures. As Arshkeyt, a 7 day kit is already being marketed; it is Phase 4 proof of concept study for validating its use in anal fissures.

Duration of Study:
After study initiation following Ethics Committee approval total time period taken for recruitment will be 6 weeks from the recruitment of the first patient. The total duration of study will be 12 months, including analysis and report writing.

SELECTION OF PARTICIPANTS:
4.1 Inclusion criteria:
1. Adult patients aged between 18 - 60 years of either sex.
2. Patients with a diagnosis of anal fissure
3. Patients with previous history of no treatment or only conservative treatment, consisting of sitz bath and/or isabgol powder and/or high fibre diet in the last 1 month.

4.2: Exclusion Criteria:
1. Patients having associated anal fistulas or anal fissure of various causes such as Crohn's disease, anal suppuration, abscesses (Secondary underlying causes).
2. Patients having anal or perianal malignancy.
3. Patients with diagnosis of any illness (other than anal fissure) with presentation of per-anal bleeding
4. Patients with history of > 3 recurrences of anal fissure post medical or surgical intervention.
5. Patients on oral calcium channel blockers or vasodilators like minoxidil, hydralazine or alprostadil.
6. Patients who have a history of topical therapy with nitroglycerine/ lignocaine/ steroids/ calcium channel blockers in the past one month.
7. Patients who are pregnant or lactating.

8. Patients with history of life threatening cardiovascular and /or neurological event in the past one year.

9. Patients with auto-immune disease, uncontrolled hypertension, uncontrolled diabetes mellitus(requiring change in antidiabetic therapy every 3 months) and chronic severe respiratory disease.

10. Patients with documented evidence of renal function tests > 1 and a half times of normal reference range at baseline visit

11. Patients withdocumented evidence of liver function tests > 2 and a half times of normal reference range at baseline visit

12. Patients with history of HIV/HBV/HCV infection in the past.

13. Patients on herbaceutical medication since the last 3 months.

14. Patient allergic to any of the ingredients of trial drug.

15. Patients currently participating in another clinical trial for any indication or has participated in any clinical trial in the last 30 days.

16. Patient not willing to sign on the informed consent document or not willing to come for follow-up visits.

Duration of subject participation:
The duration of study participation of each subject is 6 weeks. This period takes into consideration the screening visit and the window period given for each of the subsequent visits.
After a baseline assessment of the variables, each participant will be followed up at 2 weeks, 4 weeks and 6 weeks and all the variables will be noted at the visits.

STUDY MEDICATION:

The test drug will be provided by Solumiks Herbaceuticals Limited, which is manufactured according to GMP standards. The test drug will be in the form of a Arshkeyt, a 7 day kit.

The components of Arshkeyt, a "7 day kit" are as follows:
A. Arshkeyt Tablets: 7 strips each 6 Tablets
B. Arshkeyt Cream: A lamitube of 25 g Cream with an applicator.
C. Arshkeyt Powder: 7 sachets each 4 g

Packing and labeling:

Study drugs (including the test and the standard treatment) will be supplied by the sponsor in the form of a kit. It will bear study code, expiry date, name of the sponsor, batch number of the drug storage conditions and the statement "For Clinical Trial Use Only".

Storage conditions:
The study drug will be stored at the trial site in secure area with access restricted to the investigator and to qualified delegated personnel. The drugs will be stored at room temperature.

Administration schedule:
Patients will be given Arshkeyt, a 7 day kit for 6 weeks and will be advised to take the daily dose as follows:

Arshkeyt Tablets: 2 tablets thrice a day with sufficient lukewarm water.

Applicator Cream: To be applied at least twice a day and after each act of defecation with the help of the applicator. Wash the applicator with soap and warm water thoroughly and keep it dry for reuse.

Sachet Powder: One sachet to be taken at bed time with sufficient lukewarm water.

Concomitant medications:
If the patient is suffering from any other illness for which he/she is receiving drugs, he/she may be included in the study, provided such medication will not interact with the study drug. Administration of such medication must be documented in the CRF.

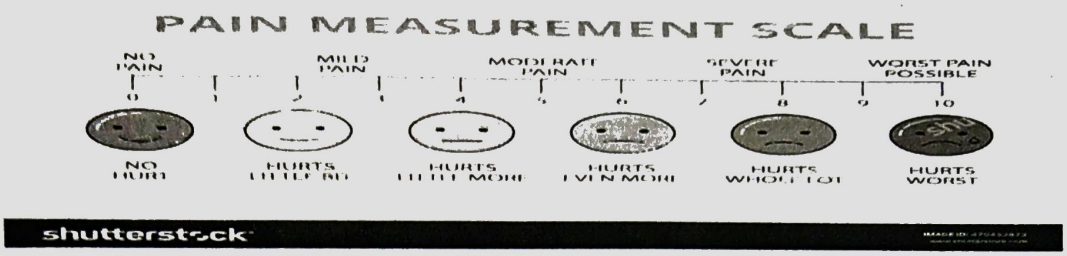
At each visit the investigator will obtain any information about intercurrent illness(es) and concomitant medication. Medication which is necessary, and which does not interact with the study drug will be given and recorded in CRF.

Withdrawal criteria (Any of the following):

1. Serious adverse events/reactions where continuation of the patient in the study poses a serious risk to the patient (according to ICH-E definition).
2. If, in the opinion of the surgeon, the patient has no option other than surgical intervention for relief, the indications may include
- Presence of external anal tag
- Presence of visible haemorrhoid
- Exposure of internal sphincter fibres at the floor of the fissure
- Infected base of fissure
- Underlying anal fistula present
3. Patient's composite score increases by 30% as compared either to the baseline composite score or the composite score at the previous visit, which ever higher.
4. Patient is unable to tolerate the test drugs.
5. Patient request for withdrawal.
6. At the discretion of principal investigator or clinician if he thinks that it is in the interest of the patient.
7. Need to use any drugs during study, which may interfere with assessment or influence the outcome.
8. Patient becomes pregnant during the course of the trial.
9. Presence of any of exclusion criteria during trial.
10. Patients having a mean percentage compliance of less than 80% or more than 120% for all the dosage form.

In case of withdrawals or dropouts, the investigator will assess the patient clinically and the reason for discontinuation from the study would be entered into the CRF.

ASSESSMENT OF EFFICACY:
8.1 Efficacy Variables:
Pain :
Intensity of pain on Self gradation scale will be recorded according to the patient's self assessment. Pain will be assessed according to VAS



ii. Bleeding per anus:

- **Streak of fresh blood :-**Grading will be done as
  0 = Absent
  1 = Present
- **Itching :-**Grading will be done as
  0 = Absent
  1 = Present
- **Constipation : -** Grading will be done as
  0 = Absent
  1 = Present

Assessment of sphincter spasm :-

Gradation of sphincteric spasm will be done on the basis of per rectal finger examination-

0 = Normal - No tightness of anal sphincter
1 = Mild - Tight anal sphincter
2 = Moderate - Due tightness of anal sphincter
3 = Severe - P/R digital examination not possible due to tightness of anal sphincter.

Ulcer

Grading will be done as
0 = Absent
1 = Present

Efficacy end-points:

Primary efficacy end-point:

Number of patients of anal fissure showing a 90% reduction in the composite score at the end of week 6.

Secondary efficacy end-point:

1 Number of patients showing significant decrease in the composite scores at the end of week 6.

2. Number of patients showing a reduction in the VAS score to < 2 from baseline to 6 weeks

3. Number of patients showing complete healing of the anal fissure wounds from baseline to 6 weeks.

4. Number of patients showing complete resolution of per-anal bleeding during defecation (grade 0) from baseline to 6 weeks.

ASSESSMENT OF SAFETY:

Safety Endpoints:

1. Number of patients showing adverse event from baseline to 6 weeks.
2. Number of patients showing abnormal physical examination findings from baseline to 6 weeks.

Specification of safety parameters:

Evaluations will be performed as specified in the visit wise schedule to assess the safety of the study drug which include:

1. General examination
2. Systemic Examination
3. Adverse event recording

General examination:

General examination will be carried out on baseline visit (week 0), at end of week 2, at end of week 4 and at the end of week 6. The various parameters which will be assessed are:
Weight (kg), temperature (0Ć), pulse rate (beats/min), blood pressure (mm of Hg), respiratory rate (per minute).
It will be scored as: Normal: 0
Abnormal: 1
Abnormality in any one of the above parameters will be scored as abnormal (score: 1)

Systemic Examination:

Systemic examination will be done by the assessor surgeon. Any abnormal systemic examination finding will be noted down by the assessor.

Adverse events (AEs)

AEs will be recorded starting from signing the ICD until the end of study. Subjects will be asked non-leading questions to determine the occurrence of AEs.

STATISTICS:

Sample size considerations:

This is a proof-of-concept study to validate the use of Arshkeyt, a 7 day kit in anal fissures hence it is pilot study and no formal sample size calculation was done. We plan to completely evaluate 30 patients of anal fissure at the end of study period. Considering a drop-out rate of 20%, we will be enrolling maximum 36 patients.

Statistical Analysis:

Chi-square test would be used for comparing the number of patients who have achieved primary and/or secondary end point.
Descriptive analysis will be used to know the percentage of patients with various points on VAS as well as various grades used for assessing bleeding and healing.
For adverse reaction comparison chi-square test will be applied and if any value in the observation is less than 5 then Fischer exact test will be applied.
For global assessment parameters, Wilcoxon signed rank test will be used. For all other assessment summary statistics will be used.
The significance level of $P < 0.05$ is used in this study

Ethics Description of ethical considerations relating to the trial: Ethical clearance will be taken from both institutions that is Parul institute of Ayurveda and Parul institute of Ayurveda and Research. CTRI registration will be done for the study.

Data Handling and Record Keeping: Data of the study will be maintained for 5 years at the study site after completion of the trial.

Insurance Financing: Study will be covered under clinical trial liability insurance scheme. The sponsor bares the responsibilities of providing copy of insurance policy that is available with the sponsor and that covers the proposed trial.

Publication Policy: The outcome of the study will be published in SCOPUS/PUBMED Indexed Journal and authorship will be shared among sponsor, principle investigator and Co-investigators. Publication cost will be borne by the sponsor.

Annexure IB

Clinical Study Protocol

Protocol title: A prospective, randomized, comparative, parallel, 2- arm study to evaluate the efficacy and safety of a Myostaal liniment application as add on therapy for the reduction of spasticity in patients suffering from Hemiplegia.

Name and address of the sponsor: Solumiks Herbaceuticals Ltd
135 Nanubhai Desai Road, Khetwadi,
Mumbai - 400 004

Principal investigator

1) Dr.Hemanth Toshikane
   Dean, Faculty of Ayurved, Parul University

Co-investigator

1) Dr.Sangeeta H .Toshikane
   Professor, Department of Panchakarma, Parul Intitute of Ayurved, Parul University
2) Dr.Divya B
   Assistant Professor, Department of Panchakarma, Parul Intitute of Ayurved & Research, Parul University
3) Dr.Chaitali Shah
   Professor, Parul Institute of Physiotherapy, Parul University

Trial site(s):

Site 1: Parul Institute of Ayurved, Parul University, AP Limda, Tal Waghodia, Vadodara, Gujarat 390019

Site 2: Parul Institute of Ayurved and Research, Parul University, AP Ishwarpura, Tal Waghodia, Vadodara, Gujarat 390019

Clinical laboratory

Site 1: Central Laboratory, Parul Ayurved Hospital, Parul University, AP Limda, Tal Waghodia, Vadodara, Gujarat 390019

Site 2: Central Laboratory, Parul Institute of Ayurved and Research, Parul University, AP Ishwarpura, Tal Waghodia, Vadodara, Gujarat 390019

Background Information: Stroke is the second leading cause of death amongst the persons above 60years of age, the fifth leading cause of death among 15-59 years old population and the leading cause of disability worldwide. According to WHO 15 million people suffer from stroke worldwide each year(WHO 2002). In India stroke prevalence rate 84-262/100000 in rural; 334-424/100000 in urban area. Mid cerebral artery is the most common vascular lesion in cerebro vascular accidents. In stroke when the injured area of brain controls Muscle tone, spasticity occurs. Effect of spasticity includes Stiff fingers, arm or legs affecting function of the muscles and mobility of joints. Each person of stroke requires a comprehensive rehabilitation programme to help them regain their quality of life; this involves a multidisciplinary team approach with inputs from physician, physiotherpaists. Physiotherapy enables people to relearn lost abilities and regain independence. Massage therapy aims to prevent stiffness of affected limbs.

Objectives

- **Primary Objective**

  1. To evaluate the efficacy in terms of reduction in the spasticity of muscles of upper limb in terms of **Tardieu scale** from baseline to day 30 with Myostaal liniment application along with physiotherapy and internal medications in patients suffering from hemiplegia in comparison to only physiotherapy in given group.

- **Secondary Objective**

  1. To evaluate the efficacy in terms of **Goniometer** to assess the range of movement of affected shoulder joint, elbow joint and wrist joint from baseline to day 30 with Myostaal liniment application along with physiotherapy in patients suffering from hemiplegia in comparison to only physiotherapy given group.
  2. To evaluate the overall improvement in patient by Patient's **Global assessment score and Physician's global assessment.**
  3. To compare the number of patients tolerating the medication and **showing score 0 in the Patient's Global safety assessment score** and **Physician's Global safety assessment score** from baseline to day 30 in both the groups.
  4. To compare the number of patients showing adverse event from baseline to day 30 in both the groups.

Trial Design: A prospective, randomized, comparative, parallel, 2-arm study

Schematic diagram:

1	Product	Myostaal Liniment
2	Indication	Hemiplegia (Whole body Massage)
3	Study Indication	Hemiplegia
4	Claims/Points	• Reduction in the spasticity of the muscles. • Improvement in the Range of movement of the joints. • Tolerability
5	Specific Investigation /Tests	**Investigations:**(Before &after treatment) • Complete blood count • RBS

		• Urinalysis
6	Study type	• Comparative (Physiotherapy Vs Massage + Physiotherapy)
7	Sample size	36 will be included to get at least 30 patients to complete the study [15 in each group]
8	Study duration	12 MONTHS, Treatment duration -30 days.
9	Product Information	**Myostaal Liniment**is a proprietary Ayurved preparation in the market for over 40 years and is widely used by healthcare practitioners in the management of Knee Osteoarthritis. The important attributes of its ingredients are as follows: **Mahanarayan Tel** improves the tone of periarticular muscles, maintains joint alignment and therefore enhances the functional efficiency of the joint. **Nirgundi (*Vitex negundo*) Tel, Gandapura (*Gaultheria fragrantissima*) &Devadaru (*Cedrus deodara*8)** relieves pain and stiffness.
10	Composition of Mayostaal	Each 10 ml contains: ✓ Mahanarayan Tel4.0 ml ✓ Nirgundi Tel (Oil of Vitex negundo)4.0 ml ✓ Gandapura Tel (Oil of Gaultheria fragrantissima)1.0 ml ✓ Tailaparna [Nilgiri] Tel (Oil of Eucalyptus globulus) 0.5 ml ✓ Devadaru Tel (Oil of Cedrusdeodara)0.3 ml ✓ Sarala [Gandhabiroja] (Pinus longifolia)0.2 gm
11	Directions for use	100 ml of Myostaal liniment will be massaged on affected body part for 30 days followed by Ushna jala snaana. Standard Ayurvedic oral treatment

A description of the trial treatment(s) and the dosage and dosage regimen of the investigational product(s):

Subjects will be given Abhyanga (body massage) with Myostaal liniment (100 ml) on affected body part for the duration of 30 minutes followed by hot water bath once per day.

The expected duration of subject participation, and a description of the sequence and duration of all trial periods, including follow-up, if any:

- 30 diagnosed Patients of Hemiplegia with MCA (middle cerebral artery) stroke fulfilling inclusion criteria after screening will be divided into two equal groups(15 in each group) by computerized randomization technique irrespective of age, gender, caste

Group A: 15 patients

- Subjects will be given Abhyanga (body massage) with Myostaal liniment (100 ml) on affected body part for the duration of 30 minutes followed by hot water bath once per day.
-
- They will given physiotherapy exercises for 5 days in week(Monday to Friday)
- a) Arm exercises- 5 exercises with 5 repetition each for one month
  1) Inner arm stretch
  2) Wrist & Hand stretch

3) Elbow stretch
4) Crawling stretch
5) Wrist motion

- b) Hand exercise:- for large grip:-with 5 repetition of each exercise in 1st & 2nd week.
  1) Hook grip
  2) Cylindrical grip
  3) Large spherical
  4) Small spherical
  5) Peg board activities

For fine grip:- with 5 repetition of each exercise in 3rd & 4th week
1) Pinch grip
2) Pulp grip
3) Making 0's
4) Intrinsic grip
5) Striking exercise

Group B: 15 patients

- Subjects will be given only physiotherapy in same way as group A subjects.

- Patients of both the groups will be given physiotherapy treatment to the affected part, they will assessed by using Tardiu scale and range of movements by Goniometer over affected upper limb.
- Acute patients (duration>1 month) will be monitored daily and recorded.

Concomitant medications: Will be continued and recorded in CRF.
Subjects will be assessed Day 0 (baseline), Day 15 ± 3, Day 30 ± 3.

A description of the "stopping rules" or "discontinuation criteria" for individual subjects, parts of trial and entire trial.

If the patient is having some serious adverse effects, allergy or any life-threatening event then the patient will be withdrawn immediately from the study.

Accountability procedures for the investigational product(s), including the placebo(s) and comparator(s), if any: Physiotherapy Regime used for haemiplagia will be advised to all subjects in both groups

Selection and Withdrawal of Subjects:
1. Subject Inclusion criteria:

1. Patient of either sex in the age group of 30-70 years.
2. Diagnosed case of Hemiplegia who is stable after onset up to 01 year.
3. Patients willing to give written informed consent.
4. Patients willing to follow up.

2. **Subject Exclusion Criteria:**

1. Comatose patients.
2. Patient on : (a) oral multi-vitamin therapy within the previous 07 days, or (b) intramuscular multiviatmins within 07 days, or (c) Oral protein suppliments which claims to enhance the muscle power, or (d) topical corticosteroid at the site of application within 14 days; Or patient requiring systemic corticosteroids during the course of study. (e) Patients on NSAIDS use will be excluded
3. Patient who has undergone cranial surgery or who is planning to undergo surgery in next 1 month will be excluded from the study.
4. Patients suffering from cerebral and cerebellar atrophy due to infectious diseases like encephelitis.
5. Patient with space occupying lesions and known case of Epilepsy.
6. Patients with auto-immune disease, uncontrolled hypertension,
7. Diabetes mellitus requiring insulin injections, chronic severe respiratory disease and severe active infectious disease requiring hospitalization.
8. Patient with history of any other systemic illness, life threatening cardiovascular and other progressive neurological diseases.
9. Patient with history of severe allergy or anaphylactic reaction.
10. Patient participating in another investigational drug trial in the previous 30 days.
11. Patients who cannot give valid consent such as mentally retarded, unconscious patients and psychiatric illness
12. History of HIV, Hepatitis B or any immune deficient conditions

Subject withdrawal criteria (i.e. terminating investigational product treatment/trial treatment) and procedures specifying:

(a) When and how to withdraw subjects from the trial/ investigational product treatment:- If the patient is having some serious adverse effects, allergy or any life-threatening event then the patient will be withdrawn immediately from the study.

(b) The type and timing of the data to be collected for withdrawn subjects:- Data of the patients who completed the complete duration of the treatment will be considered for the statistical analysis

(c) Whether and how subjects are to be replaced.

(d) The follow-up for subjects withdrawn from investigational product treatment/trial treatment.

A)Medication(s)/treatment(s) permitted (including rescue medication) and not permitted before and/or during the trial.

Concomitant Medicine:

If patient is on any concomitant medicine such as anti-hypertensive or antidiabetic those will documented accordingly and analysed.

Assessment of Efficacy Specification of the efficacy parameters, Methods and timing for assessing, recording, and Analyzing of efficacy parameters:

i. Efficacy parameters –

Tardieu Scale to assess the spasticity, Goniometer to assess the Range of movement of affected shoulder joint, elbow joint and wrist joint – Day 0 ± 3, Day 15 ± 3, Day 30 ± 3.

ii. Safety parameters –

Patients global safety assessment score and Adverse events recording – Day 15 ± 3, Day 30 ± 3.

Assessment of Safety Specification of safety parameters:

A) Patient's Global safety assessment score:

a) Poor: severe adverse effects which required discontinuation of therapy.

b) Fair: moderate adverse effects but therapy was continued following symptomatic treatment for adverse effect

c) Good: mild adverse effects but possible to continue therapy without giving any treatment mild adverse effects but possible to continue therapy without giving any treatment
d) Excellent: no adverse effects.

B) Adverse events recording

Statistics:

- Data will be analysed using SPSS version software.
- Descriptive statistics will be assessed.
- Data will be expressed in percentages and Mean + SD.
- Data in a group at two intervals will be compared using paired t test (data with normal distribution)/ Wilcoxon signed rank test (data with non-normal distribution).
- Data between two groups will be compared using unpaired t test (data with normal distribution) / Mann Whitney test (data with non-normal distribution).
- Data in a group at 3 or more intervals will be compared using repeated measures ANOVA (data with normal distribution)/ Friedman test (data with non-normal distribution).

Chi-square test would be used for comparing the number of patients who have achieved primary and/or secondary end point.

- For adverse reaction comparison chi square test will be applied and if any value in the observation is less than 5 then Fischer exact test will be applied.
- The level of significance in the study will be 0.05.

Ethics Description of ethical considerations relating to the trial:
Ethical clearance will be taken from both institutions that is Parul institute of Ayurveda and Parul institute of Ayurveda and Research. CTRI registration will be done for the study.

Data Handling and Record Keeping: Data of the study will be maintained for 5 years at the study site after completion of the trial.

Insurance Financing: Study will be covered under clinical trial liability insurance scheme. The sponsor bares the responsibilities of providing copy of insurance policy that is available with the sponsorer and that covers the proposed trial.

Publication Policy: The outcome of the study will be published in SCOPUS/PUBMED Indexed Journal and authorship will be shared among sponsor, principle investigator and Co-investigators. Publication cost will be borne by the sponsor.

Annexure IC

Study Protocol

Protocol title:

A prospective, randomized, comparative, parallel, 2-arm study to evaluate the efficacy and safety of a Myostaal liniment application as add on therapy for muscle strengthening in patients suffering from osteoarthritis of knee

Name and address of the sponsor: Solumiks Herbaceuticals Ltd

135 Nanubhai Desai Road, Khetwadi,
Mumbai - 400 004

Principal investigator

1) Dr. Shailesh Deshpande
Professor, Department of Kayachikitsa, Parul Intitute of Ayurved, Parul University

Co-investigator

1) Dr. Vaishali Deshpande
Professor, Department of Kayachikitsa, Parul Intitute of Ayurved & Research, Parul University
2) Dr. Teja Naik
Assistant Professor, Department of Kayachikitsa, Parul Intitute of Ayurved & Research, Parul University

Trial site(s):

Site 1: Parul Institute of Ayurved, Parul University, AP Limda, Tal Waghodia, Vadodara, Gujarat 390019

Site 2: Parul Institute of Ayurved and Research, Parul University, AP Ishwarpura, Tal Waghodia, Vadodara, Gujarat 390019

Clinical laboratory

Site 1: Central Laboratory, Parul Ayurved Hospital, Parul University, AP Limda, Tal Waghodia, Vadodara, Gujarat 390019

Site 2: Central Laboratory, Parul Institute of Ayurved and Research, Parul University, AP Ishwarpura, Tal Waghodia, Vadodara, Gujarat 390019

Background Information:

Osteoarthritis (OA) is the most prevalent form of arthritis in India and it is estimated to affects over 15 million adults every year. Osteoarthritis continues to have serious impact on the lives of elderly people but in the last few decades, Indians in the age-group of 30 to 50 years are falling prey to this disease. By 2025, India is estimated to be the Chronic Disease Capital with 60 million people suffering from arthritis.

Conventional treatments for OA include pain medication (nonsteroidal anti-inflammatory drugs and cyclooxygenase-2 inhibitors), exercises, hot and cold therapy, corticosteroid injections and eventually, surgery to repair the joint. Despite conventional treatment, OA is often progressive and frequently leads to chronic pain and disability.3

In osteoarthritis, NICE (National Institute of Health and Care Excellence) Guidelines, United Kingdom, recommends exercise as a core treatment, irrespective of age, comorbidity, pain severity or disability. Exercise should include local muscle strengthening and general aerobic fitness.4

In Ayurved Massage is done with medicated oils like Mahanarayan Tel are widely used by Ayurved practitioners to improve the tone of periarticular muscles.

10. Trial Objectives and Purpose A detailed description of the objectives and the purpose of the trial:

- **Primary Objective**

  To evaluate the efficacy in terms of change of Assessment of Knee Muscle Strength by **Dynamometer** from baseline to day 90 with Myostaal liniment application along with physiotherapy in patients suffering from knee joint osteoarthritis in comparison to only physiotherapy given group

- **Secondary Objective**

  1.To evaluate the efficacy in terms of change of WOMAC functional sub-scale score (at least 2 grades) from baseline to day 90 with Myostaal liniment application along with physiotherapy in patients suffering from knee joint osteoarthritis in comparison to only physiotherapy given group

  2. To evaluate the efficacy in terms of change in **distance covered in 6 minutes' walk test** from baseline to day 90 with Myostaal liniment application along with physiotherapy in patients suffering from knee joint osteoarthritis in comparison to only physiotherapy given group.

  3. To evaluate the efficacy in terms of **time assessment in single leg stand test** from baseline to day 90 with Myostaal liniment application along with physiotherapy in patients suffering from knee joint osteoarthritis in comparison to only physiotherapy given group.

  4.To evaluate the efficacy in terms of **time assessment in 5 times sit to stand test duration** from baseline to day 90 with Myostaal liniment application along with physiotherapy in patients suffering from knee osteoarthritis in comparison to only physiotherapy given group.

  5. To evaluate the efficacy in **terms of Visual Analogue Scale** with Myostaal liniment application along with physiotherapy in patients suffering from knee osteoarthritis, from baseline to day 90 at the final visit in comparison to only physiotherapy given group.

  6. To evaluate the efficacy in **terms of WOMAC pain sub-scale score** with Myostaal liniment application along with physiotherapy in patients suffering from knee joint osteoarthritis from baseline to day 90 visit in comparison to only physiotherapy given group.

7. To evaluate the efficacy in **terms of the WOMAC stiffness sub-scale score**, with Myostaal liniment application along with physiotherapy in patients suffering from knee joint osteoarthritis from baseline to day 90 visit in comparison to only physiotherapy given group.

8. To evaluate the efficacy in terms of the **Lequesne severity index score** with Myostaal liniment application along with physiotherapy in patients suffering from knee osteoarthritis from baseline to day 90 at the final visit in comparison to only physiotherapy given group.

9. To evaluate the overall improvement in patient by Patient's **Global assessment score.**

10. To compare the number of patients tolerating the medication and **showing score 0 in the Patient's Global safety assessment score** from baseline to day 90 in both the groups.

11. To compare the number of patients showing adverse event from baseline to day 90 in both the groups.

Trial Design: A prospective, randomized, comparative, parallel, 2-arm study

Schematic diagram of trial design, procedures, stages and treatment in subjects:

GROUP A	GROUP B
Myostaal liniment application along with Physiotherapy	Physiotherapy
Duration: 90 days	Duration: 90 days
Dose: 5 ml for each knee	-
Frequency: Twice per day	

1	Product	Myostaal Liniment
2	Indication	Osteoarthritis (Local Application for Massage)
3	Study Indication	Knee Osteoarthritis
4	Claims/Points	• Improvement in Knee Muscle Strength / Quaricep Muscle Strenghening • Symptomatic Improvement (in Pain, Stiffness & Physical Function) • Tolerability
5	Specific Investigation /Tests	• Assessment of Knee Muscle Strength by Dynamometer. **Investigations:** (BEFORE &AFTER TREATMENT) • Hb%

		• RBS, FBS,PPBS if needed • Urine Routine & Microscopy • UPT (In child bearing patients) (BEFORE TREATEMNT) • KNEE X-RAY AP, LATERAL
6	Study type	• A prospective, randomized, comparative, parallel, 2-arm study
7	Sample size	72 will be included to get at least 60 patients to complete the study [30 in each group]
8	Study duration	3 MONTHS
9	Product Information	**Myostaal Liniment**is a proprietary Ayurved preparation in the market for over 40 years and is widely used by healthcare practitioners in the management of Knee Osteoarthritis. The important attributes of its ingredients are as follows: **Mahanarayan Tels**improve the tone of periarticular muscles, maintains joint alignment and therefore enhance the functional efficiency of the joint. **Nirgundi (*Vitex negundo*) Tel, Gandapura (*Gaultheria fragrantissima*) &Devadaru (*Cedrus deodaras*)** relieve joint pain, swelling and overcome morning stiffness.
10	Composition of Mayostaal	Each 10 ml contains: ✓ Mahanarayan Tel4.0 ml ✓ Nirgundi Tel (Oil of Vitex negundo)4.0 ml ✓ Gandapura Tel (Oil of Gaultheria fragrantissima)1.0 ml ✓ Tailaparna [Nilgiri] Tel (Oil of Eucalyptus globulus) 0.5 ml ✓ Devadaru Tel (Oil of Cedrusdeodara)0.3 ml ✓ Sarala [Gandhabiroja] (Pinus longifolia)0.2 gm
11	Directions for use	Five ml liniment to be massage on the both affected knee twice daily

A description of the measures taken to minimize/avoid bias, including:

(a) Randomization:Permuted Computerised Block Randomization Method.

(b) Blinding: No Blinding.

A description of the trial treatment(s) and the dosage and dosage regimen of the investigational product(s):5 ml liniment to be massage on the affected knee twice daily

Also include a description of the dosage form, packaging, and labelling of the investigational product(s): As Mayostaal liniment is already marketed and the given study is an open label non blinded, so no any specific labeling will be done and the product will be as such given to the patient.

The expected duration of subject participation, and a description of the sequence and duration of all trial periods, including follow-up, if any: 3 MONTHS with follow up sequence days- Follow up will be done every 15 days once ± 5 Days

Day 0 ± 5, Day 15 ± 5, Day 30 ± 5, Day 45 ± 5, Day 60 ± 5 , Day 75 ± 5 , Day 90 ± 5

A description of the "stopping rules" or "discontinuation criteria" for individual subjects, parts of trial and entire trial: If the patient is having some serious adverse effects, allergy or any life-threatening event then the patient will be withdrawn immediately from the study.

Accountability procedures for the investigational product(s), including the placebo(s) and comparator(s), if any: Physiotherapy Regime used for osteoarthritis of knee will be advised to all subjects in both groups

Maintenance of trial treatment randomization codes and procedures for breaking codes: There is no any code as the study is randomized

Selection and Withdrawal of Subjects:

I. **Subject Inclusion criteria**:

1.Patient of either gender in the age group of 40-70 years.

2. Diagnosed case of Idiopathic knee osteoarthritis for minimum 1month and maximum 5 years according to clinical guidelines of American college of Rheumatology. The guidelines include patient currently experiencing pain in one or both the knees with at least 3 out of the following 6 features:

- Age 40 – 70 years

- Morning stiffness within 30 minutes of walking

- Crepitus

- Bony tenderness

- Bony enlargement

- No palpable warmth

3. Patient having baseline knee joint pain more than 40 mm on Visual Analogue Scale (VAS) either at rest or on weight bearing activities (e.g. walking, standing, climbing staircase) during the preceding 24 hours.

4.Patients who have Grades 1 and 2 in radiological findings.

7. Patients willing to give written informed consent.

8. Patients willing to follow up.

II. Subject Exclusion Criteria:

1. Patient with secondary arthritis related to systemic inflammatory

arthritis (including rheumatoid arthritis, psoriatic arthritis, post infectious arthritis and metabolic arthritis, traumatic arthritis or

surgical joint replacement)

2. Patient on corticosteroid use:

(a) oral corticosteroid within the previous 14 days;

(b) intramuscular corticosteroid within 30 days;

(c) intra-articular corticosteroid into the study knee within 90 days;

(d) intra-articular corticosteroid into any other joint within 30 days;

(e) topical corticosteroid at the site of application within 14 days; Or patient requiring systemic corticosteroids during the course of study;

(f) Patients on NSAIDS use will be excluded;

3. Patient who has undergone or who is planning to undergo surgery in next 3 months will be excluded from the study;

4. Patient who has underwent knee replacement surgery for the affected knee and who hasundergone a knee arthroscopy within past 3 years. Also, Patient with intra-articular visco supplementation (e.g., Synvisc®) in the affected knee joint in the preceding 6 months;

5. Patient with on-going use of medication including oral muscle relaxants, or low dose antidepressant for any chronic pain Management;

6. Patients with auto-immune disease, uncontrolled hypertension, Diabetes mellitus requiring insulin injections and chronic severe respiratory disease;

7. Patient with history of clinically active renal, hepatic or peptic ulcer disease;

8. History of life threatening cardiovascular and /or neurological event in the past one year;

9. Patient with history of alcohol or drug abuse, bleeding disorder;

10. Patient having any severe active infectious disease requiring hospitalization;

11. Pregnancy or lactation;

13. Patient with history of severe allergy or anaphylactic reaction;

13. Patient participating in another investigational drug trial in the previous 30 days.

14. Patients who cannot give valid consent such as mentally retarded, unconscious patients and psychiatric illness.

15. Known history of positive screening result for hepatitis B and/or Hepatitis C virus.

16. History of HIV or any immune deficient conditions.

Subject withdrawal criteria (i.e. terminating investigational product treatment/trial treatment) and procedures specifying:

(a) When and how to withdraw subjects from the trial/ investigational product treatment.: If the patient shows serious allergic reaction after application of mayostaal liniment,patient will be immediately withdrawn.

(b) The type and timing of the data to be collected for withdrawn subjects.: It will be mentioned in the CRF itself.

(c) Whether and how subjects are to be replaced:A new case will be registered against the withdrawn case.

(d) The follow-up for subjects withdrawn from investigational product treatment/trial treatment: Unless and until the patient is relievedfrom the adverse symptoms occurred due to the application,the patient will be on followup.

Rescue medicine of Subjects:

A) Medication(s)/treatment(s) permitted (including rescue medication) and not permitted before and/or during the trial

- **Rescue medicine**:

Paracetamol 500mg – Details regarding frequency of dosage, number of days, indicators etc will be recorded.

- **Concomitant Medicine:**

If patient is on any concomitant medicine such as anti-hypertensive or antidiabetic those will documented accordingly and analysed.

Assessment of Efficacy Specification of the efficacy parameters, Methods and timing for assessing, recording, and Analyzing of efficacy parameters:

i. Efficacy parameters –

Knee assessment with Dynamometer, WOMAC scores, 6 Minutes' walk test, Single leg stance test, 5 times sit to stand test, VAS score, Lequesne severity index score – Day 0 ± 5, Day 15 ± 5, Day 30 ± 5, Day 45 ± 5, Day 60 ± 5 , Day 75 ± 5, Day 90 ± 5

ii. Safety parameters –

Patients global safety assessment score and Adverse events recording – Day 0 ± 5, Day 15 ± 5, Day 30 ± 5, Day 45 ± 5, Day 60 ± 5 , Day 75 ± 5, Day 90 ± 5

Assessment of Safety Specification of safety parameters:

A) Patient's Global safety assessment score:

a) Poor: severe adverse effects which required discontinuation of therapy.

b) Fair: moderate adverse effects but therapy was continued following symptomatic treatment for adverse effect

c) Good: mild adverse effects but possible to continue therapy without giving any treatment mild adverse effects but possible to continue therapy without giving any treatment

d) Excellent: no adverse effects.

B) Adverse events recording

Statistics:

- Data will be analysed using SPSS version software.
- Descriptive statistics will be assessed.
- Data will be expressed in percentages and Mean + SD.
- Data in a group at two intervals will be compared using paired t test (data with normal distribution)/ Wilcoxon signed rank test (data with non-normal distribution).
- Data between two groups will be compared using unpaired t test (data with normal distribution) / Mann Whitney test (data with non-normal distribution).
- Data in a group at 3 or more intervals will be compared using repeated measures ANOVA (data with normal distribution)/ Friedman test (data with non-normal distribution).

Chi-square test would be used for comparing the number of patients who have achieved primary and/or secondary end point.

- For adverse reaction comparison chi square test will be applied and if any value in the observation is less than 5 then Fischer exact test will be applied.
- The level of significance in the study will be 0.05.

Ethics Description of ethical considerations relating to the trial: Ethical clearance will be taken from both institutions that is Parul institute of Ayurveda and Parul institute of Ayurveda and Research. CTRI registration will be done for the study.

Data Handling and Record Keeping: Data of the study will be maintained for 5 years at the study site after completion of the trial.

Insurance Financing: Study will be covered under clinical trial liability insurance scheme. The sponsor have the responsibilities of providing copy of insurance policy that is available with the sponsor and that covers the proposed trial.

Publication Policy: The outcome of the study will be published in SCOPUS/PUBMED Indexed Journal and authorship will be shared among sponsor, principle investigator and Co-investigators. Publication cost will be borne by the sponsor.

Annexure ID

Clinical Study Protocol

Protocol title: CLINICAL STUDTY TO EVALUATE EFFECT OF MENOCRAMP TABLETS IN THE MANAGEMENT OF PRIMARY DYSMENORRHOEA

Name and address of the sponsor: Solumiks Herbaceuticals Limited,
135 Nanubhai Desai Road, Khetwadi,
Mumbai - 400 004

Principal Investigator (PI)

1) **Dr. Asokan Vasudevan, Professor**
Department of Prasuti Tantra and Stree Roga, Parul Intitute of Ayurved, Parul University

Co-investigator(s)

1) **Dr. Vasanthi T, Assistant Professor,**
Department of Prasuti Tantra and Stree Roga, Parul Intitute of Ayurved and Research, Parul University.

2) **Dr. Akanksha, Associate Professor,**
Department of Obstetrics and Gynecology, Parul Sevashram Hospital, Parul University.

Trial site(s):

- Site 1: Parul Institute of Ayurved, Parul University, AP Limda, Tal Waghodia, Vadodara, Gujarat 390019
- Site 2: Parul Institute of Ayurved and Research, Parul University, AP Ishwarpura, Tal Waghodia, Vadodara, Gujarat 390019

Clinical laboratory:
Site 1: Central Laboratory, Parul Ayurved Hospital, Parul University, AP Limda, Tal Waghodia, Vadodara, Gujarat 390019

Site 2: Central Laboratory, Parul Institute of Ayurved and Research, Parul University, AP Ishwarpura, Tal Waghodia, Vadodara, Gujarat 390019

Background Information

Introduction: Spasmodic Dysmenorrhea means painful menstruation which can be correlated with *udavartini yonivyapad* of charaka or Udavarta of sushruta. Udavarta[1] is explained in Ayurveda as a Nanatmaja Vata vyadhi by Charaka where there is abnormal movement of Vayu in Pakwashaya. According to Charaka, Rajas(Artava) is pushed in upward direction by the aggravated Apana Vayu due to obstruction in its normal flow (Anuloma Gati) in Pakwashaya[3], the chief site of Apana Vayu. Incidence is 50% of post-pubescent females managed with NSAID'S which may have adverse effects in sensitive individuals, which restrict their use. Therefore, a complete, comprehensive and holistic approach toward

Annexure ID

Clinical Study Protocol

Protocol title: CLINICAL STUDY TO EVALUATE EFFECT OF MENOCRAMP TABLETS IN THE MANAGEMENT OF PRIMARY DYSMENORRHOEA

Name and address of the sponsor: Sahumika Herbaceuticals Limited,
133 Nanubhai Desai Road, Kherwadi,
Mumbai - 400 004

Principal Investigator (PI)

1) **Dr. Archana Vasudevan, Professor,**
Department of Prasuti Tantra and Stree Roga, Parul Istitute of Ayurved, Parul University

Co-investigator(s)

1) **Dr. Vasavda K., Assistant Professor,**
Department of Prasuti Tantra and Stree Roga, Parul Istitute of Ayurved and Research, Parul University.

2) **Dr. Akanksha, Associate Professor,**
Department of Obstetrics and Gynecology, Parul Sevashram Hospital, Parul University.

Trial site(s):

- Site 1: Parul Institute of Ayurved, Parul University, AP Limda, Tal Waghodia, Vadodara, Gujarat 390019
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Clinical laboratory:

Site 1: Central Laboratory, Parul Ayurved Hospital, Parul University, AP Limda, Tal Waghodia, Vadodara, Gujarat 390019

Site 2: Central Laboratory, Parul Institute of Ayurved and Research, Parul University, AP Ishwarpura, Tal Waghodia, Vadodara, Gujarat 390019

Background Information

Introduction: Spasmodic Dysmenorrhea means painful menstruation which can be correlated with *udavarta* mentioned of charaka or Udavarta of sushruta. Udavarta[1] is explained in Ayurveda as a Nanatmaja Vata vyadhi by Charaka where there is abnormal movement of Vayu in Pakwashaya. According to Charaka, Rajas(Artava) is pushed in upward direction by the aggravated Apana Vayu due to obstruction in its normal flow (Anuloma Gati) in Pakwashaya[2], the chief site of Apana Vayu. Incidence is 50% of post-pubescent females managed with NSAID'S which may have adverse effects in sensitive individuals, which restrict their use. Therefore, a complete, comprehensive and holistic approach toward

its understanding and treatment of pre menstrual syndrome and dysmenorrhoea through Vatanulomana action of Ayurveda drugs is attempted through Menocramp Tablets.

Aim:

To evaluate the effect of *Menocramp Tablets* in the management of acute phase of pain in Primary Dysmenorrhoea.

Objective:

- To evaluate the effect of drug on associate complaints of dysmenorrhoea.
- To assess the efficacy of drug in reducing the psychological complaints associated with dysmenorrhoea.

Study Design:

Open labeled, Non-Randomized, Interventional, Multi-centric, Phase IV, Post Marketing Drug Surveillance trial to evaluate effect of *Menocramp* Tablets in the management of Primary Dysmenorrhoea with proper arrangements for withdrawals.

Dosage: 2 Tab. Thrice 3 daily after food with warm water from day 1 to day 5 of menstruation for 3 months.

Assessment criteria:

Assessment of pain (dysmenorrhea):

VISUAL ANALOGUE SCALE

0 1 2 3 4 5 6 7 8 9 10

NOPAIN	Annoying (mild)	Uncomfortable (moderate)	Horrible (severe)	WORST

WaLIDD Score for dysmenorrhea

Table 1 WaLIDD score variables

Working ability	Location	Intensity (Wong–Baker)	Days of pain
0: None	0: None	0: Does not hurt	0: 0
1: Almost never	1: 1 site	1: Hurts a little bit	1: 1–2
2: Almost always	2: 2–3 sites	2: Hurts a little more – hurts even more	2: 3–4
3: Always	3: 4 sites	3: Hurts a whole lot – hurts worst	3: ≥5

Notes: Score: 0 without dysmenorrhea, 1–4 mild dysmenorrhea, 5–7 moderate dysmenorrhea, 8–12 severe dysmenorrhea. Wong–Baker scale was reclassified to adjust a four-level scale.

Abbreviation: WaLIDD, working ability, location, intensity, days of pain, dysmenorrhea.

Severity Of Pain (multidimensional scoring pattern)

Grading	Assessment
0	Menstruation is not painful and daily activity unaffected
1	Menstruation is painful and daily activity not affected. No analgesic required.
2	Menstruation is painful and daily activity affected. Analgesic drug were needed.
3	Menstruation is painful, she cannot do even her normal routine work and has to absent from class / office during menses. Had to take analgesic but poor effect.

Duration

Grading	Assessment
0	No pain in menstruation
1	Pain persist less than 12 hours
2	Pain continue for 12 -24 hours
3	Pain continue more than 24 hours

Gradation Of Associated Symptoms:

Quantity of menstrual flow (by number of pad)

Grading	Assessment
0	6 – 7 pads/cycle
1	4 – 5 pads/cycle
2	2 – 3 pads/cycle
3	Spotting or 1 pad/cycle

Quantity of menstrual flow (by interval between menstrual cycles)

Grading	Assessment
0	25-35 days
1	36-45 days
2	46-55 days
3	56-65 days

Fatigue

Grading	Assessment
0	No *Shrama* (Fatigue)
1	Fatigue by single extra work other than daily routine
2	Fatigue by normal daily routine.
3	Severe fatigue even without work

Tenesmus of the bladder (Vankshana Shoola, KatiShoolaand JaanuShoola)

Grading	Assessment
0	No pain
1.	Presence of all 03 < 1 hour / 02 features < 6 hrs / 01 feature < 12 hrs
2.	Presence of all 03 1-2 hrs/ 02 features 6-12 hrs/ 01 feature > 12 hrs
3	Presence of all 03 > 2 hrs / 02 features 12-24 hrs./ 01 feature > 24 hrs.

Swedaadhikya (Excessive sweating)

Grading	Assessment
0	No sweating
1	Occurs only at working in hot or doing hard work
2	More in day time and when associated or following hot flushes only
3	Excessive sweating to that extend that patient feels like taking bath changing clothes

Tamodarshana (Faints)

Grading	Assessment
0	No faints
1	Occasionally ones per menstruation
2	1 faint per each menstruation.
3	More than 1 times per each menstruation.

Diagnostic Criteria:

- Painful menstruation of acute and spasmodic nature
- Pain of sufficient magnitude to hamper the routine daily activities for 48 - 72 hours duration in regular menstrual cycles.
- Associated with or without constipation, loose stools, nausea, breast tenderness, mood swings, headache, giddiness, irritability.

Inclusion Criteria:

1. Women with age group of 15–30 years of either married or unmarried.

2. Women with regular cycle with painful menstruation.
3. Women without any pelvic pathology.
4. Be able and willing, in the view of the investigator, to comply with all study procedures, and sign informed written consent form.

Exclusion criteria:

1. Women aged below 15 and above 30 years
2. Married women with irregular cycles
3. Women with history of PID, endometriosis and debilitating pathological conditions of the pelvic organs, systemic diseases like diabetes mellitus, bronchial asthma, tuberculosis, thyroid dysfunction, with organic lesion (benign or malignant growth of reproductive tract), uterine prolapse and Hypo-plastic uterus.
4. Women with congenital anomalies of genital organs

Subjects fulfilling the criteria of diagnosis and inclusion will be incorporated in this trail and subjected to thorough screening, history taking and physical examination.

Laboratory Investigations:

The following investigations will be carried out on all subjects before trial and after trial in order to rule out other systemic illness and to assess the impact of the intervention.

- ✓ Routine haematological: CBC
- ✓ Urine Routine and microscopy
- ✓ Ultra Sonography: Abdominal where ever necessary.

Details of History and Examination will be recorded in a specially designed Case Proforma.

Withdrawal criteria:

- Patient not giving follow-up on 2 consecutive scheduled visit.
- Patient suffers from any adverse event during study period which is detrimental for study.

Plan of study:

Women with Primary Dysmenorrhoea will be survey screened and diagnosed with standard diagnostic parameters and selected from Out-patient Department of Prasuti Tantra and Stree Roga, Parul Ayurveda

Hospital, Vadodara as well as Parul Sevashram Hospital and Parul Hospital for Ayurveda and Research, Ishwerpura.
After informed consent process subjects will be screened as per inclusion and exclusion criteria.
Patients full filling inclusion criteria will be included in the study.

Interventions:

Target Sample Size (n): Minimum 100

Drug review

Menocramp tablet is proprietary Ayurvedic medicine manufactured by Solumix Herbaceuticals Pvt. Limited. It is used in the painful menstruation. It relieves the spasm and pain. It is a comprehensive formula in the management of dysmenorrhoea.

Benefits of Tab. Menocramp

Decreases uterine spasm

Relieves the pain

Ease the menstrual flow

Reduces the stress and mood swings

Indication

Dysmenorrhea

Premenstrual syndrome

Dosage: 2 Tab. Thrice 3 daily after food.

Anupana: Warm water

Duration: For 5 days from day 1 to day 5 of menses for 3 months (15 Days)

Each coated tablet contains extracts of

Sr.No	Drug	Bot,. Name	Proportion
1.	Ashoka	*Saraca indica*	75mg

2.	Lodhra	*Symplocos racemosa*	75mg
3.	Aswagandha	*Withania somnifera*	75mg
4.	Haritaki	*Terminalia chebula*	75mg
5.	Parashika yavani	*Hyosyamus niger*	50mg
6.	Jatamamsi	*Nardostachys jatamamsi*	50mg
7.	Shodhita Guggulu	*Commiphora mukul*	100mg
8.	Bhavana Dravya *Dashamoola* *Erandamoola* *Kumari* *Shunti*	 *Ricinus Communis* *Aloe vera* *Gingiber officinalis*	QS

Side effects

- Stomach upset
- Nausea
- Acute toxicity
- Skin rashes

Concomitant Medications:

- Medications or treatments received by patient for treatment of condition other than Iron deficiency anemia will be documented in case report form.

Statistics:
Statistical analysis will be done by applying appropriate tests.
Chi-square test will be applied to assess overall efficacy of Abhraloha

Ethics Description of ethical considerations relating to the trial: Ethical clearance will be taken from both institutions that is Parul institute of Ayurveda and Parul institute of Ayurveda and Research. CTRI registration will be done for the study.

Data Handling and Record Keeping: Data of the study will be maintained for 5 years at the study site after completion of the trial.

Insurance Financing: Study will be covered under clinical trial liability insurance scheme. The sponsorer bares the responsibilities of providing copy of insurance policy that is available with the sponsorer and that covers the proposed trial.

Publication Policy: The outcome of the study will be published in SCOPUS/PUBMED Indexed Journal and authorship will be shared among sponsorer, principle investigator and Co-investigators. Publication cost will be borne by the sponsorer.

ANNEXURE IIA

Budget for - An Open Labelled phase 4 Single Group Proof of concept study to evaluate the Efficacy & Safety of Arshkeyt, a 7 day kit in patients suffering from Anal fissures.

No.	Expenditure Head	Total Expenditure (Rs.)
1	EC Review Fees.	10000.00
2	Investigator Charges	30000.00
3	Co-Investigator Charges	30000.00
4	Research Associate Charges	10000.00
5	Lab Investigations	29520.00
6	Institutional Charges	15000.00
	Total	**124520.00**
	Installment 1 (25% at Study Initiation)	**40000.00**
	Installment 2 (25% on receipt of Interim Report)	**30000.00**
	Installment 3 (Balance 50% after receipt of Final Report)	**54520.00**

ANNEXURE IIB

Budget for - A prospective, randomized, comparative, parallel, 2- arm study to evaluate the efficacy and safety of a Myostaal liniment application as add on therapy for the reduction of spasticity in patients suffering from Hemiplegia.

No.	Expenditure Head	Total Expenditure (Rs.)
1	EC Review Fees.	10000.00
2	Investigator Charges	30000.00
3	Co-Investigator Charges	30000.00
4	Research Associate Charges	10000.00
5	Lab Investigations	16100.00
6	Institutional Charges	15000.00
	Total	**111100.00**
	Installment 1 (25% at Study Initiation)	**37000.00**
	Installment 2 (25% on receipt of Interim Report)	**26000.00**
	Installment 3 (Balance 50% after receipt of Final Report)	**48100.00**

ANNEXURE IIC

Budget for - A prospective, randomized, comparative, parallel, 2-arm study to evaluate the efficacy and safety of a Myostaal liniment application as addon therapy for muscle strengthening in patients suffering from osteoarthritis of knee.

No.	Expenditure Head	Total Expenditure (Rs.)
1	EC Review Fees.	10000.00
2	Investigator Charges	30000.00
3	Co-Investigator Charges	30000.00
4	Research Associate Charges	10000.00
5	Lab Investigations	41760.00
6	Institutional Charges	15000.00
	Total	**136760.00**
	Installment 1 (25% at Study Initiation)	**43000.00**
	Installment 2 (25% on receipt of Interim Report)	**33000.00**
	Installment 3 (Balance 50% after receipt of Final Report)	**60760.00**

ANNEXURE IID

Budget for - Clinical study to evaluate effect of Menocramp Tablets in the management of Primary Dysmenorrhoea.

No.	Expenditure Head	Total Expenditure (Rs.)
1	EC Review Fees.	10000.00
2	Investigator Charges	30000.00
3	Co-Investigator Charges	30000.00
4	Research Associate Charges	10000.00
5	Lab Investigations	34000.00
6	Institutional Charges	15000.00
	Total	**129000.00**
	Installment 1 (25% at Study Initiation)	**41000.00**
	Installment 2 (25% on receipt of Interim Report)	**31000.00**
	Installment 3 (Balance 50% after receipt of Final Report)	**57000.00**